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| EXAMINER | |
|---|---|
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| **ART UNIT** | **PAPER NUMBER** |
| 1616 | |

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/730,796 | SIX ET AL. | |
| | Examiner | Art Unit | |
| | James H. Alstrum-Acevedo | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1-20 are pending.**

### *Specification*

The disclosure is objected to because of the following informalities: the word "polyoxyethylene" is misspelled on page 6, line 16 as "polyoxtethylene."

Appropriate correction is required.

Claim 8 is objected to because of the following informalities: the word "polyoxyethylene" is misspelled on line 3 of said claim as "polyoxtethylene." Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

**Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 1 recites: "inorganic and organic acids having a pH range of 2.5-4.5 in aqueous solution." The recitation is confusing because the pH of a solution is determined by the amount of acid present (i.e. the hydronium ion concentration) and not by the kind of acid used. In other words, "pH range" is not a characteristic of an acid, but rather the quantity of acid used.

Claim 1 is also confusing, because the phrase "an acid selected from the group consisting of one or more of inorganic and organic acids..." may be interpreted different ways, such as meaning the selection of only one acid or the selection of one inorganic acid and one organic acid, etc.

Claims 2, 7, 9, 13, and 14 are indefinite for reciting ranges of amounts of components based on weight. However, it is unclear whether the weight Applicant is referring to is the weight of the total formulation, the weight of a component relative to other components, or the weight of a component prior to the addition of propellant.

The remaining claims are rejected as being dependent upon a rejected claim.

**Claim 10 recites the limitation "anhydrous crystalline form of tiotropium bromide" in lines 1 and 2.** There is insufficient antecedent basis for this limitation in the claim.

### *Claim Rejections - 35 USC § 102*

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 1-4, 6, 8, 9, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/07567).** Keller et al., U. S. Patent No. 6,475,467 is being used as the English language equivalent of WO 00/07567.

The limitation of claim 1 reciting, "inorganic or organic acids having a pH range of 2.5 to 4.5 in aqueous solution" is given no weight in this examination, because pH range is **not** a property of an acid, but rather a property of the **amount of acid used**. This has been described in greater detail above in the 35 U.S.C. § 112 rejection.

Keller discloses suspension aerosol formulations comprising pharmaceutical active compounds and cromoglycic acid and/or nedocromil as carriers (abstract).

Keller discloses preferred examples of the active compounds of his invention include **tiotropium** (col. 5, line 24) and **tiotropium bromide** (col.5, line 32). The aerosol formulations may also contain two or more pharmaceutically active compounds and combinations of fluticasone, ipratropium, oxitropium, glycopyrronium, **tiotropium**, budesonide, mometasone, ciclesonide, rofleponide or a pharmaceutically acceptable salt or derivative thereof with levalbuterol, formoterol and/or salmeterol or a pharmaceutically acceptable derivative thereof being preferred. The aerosol formulations according to the invention can also contain **dissolved active compounds**; it is only essential to the invention that **at least one pharmaceutically active compound is present in suspended form** (col. 5, lines 36-47).

Keller discloses that the weight ratio of the cromoglycic acid salts and/or nedocromil salts to the suspended pharmaceutically active compound or to the suspended pharmaceutically active compounds is approximately 10:1 to approximately 1:10 (col. 6, lines 59-64).

Keller discloses that suitable non-toxic **liquid propellants** for aerosol formulations include **hydrofluorocarbons** (i.e. HFC), specifically, difluoromethane (HFA 32), pentafluoroethane (HFA 125), **1,1,2,2-tetrafluoroethane (HFA 134), 1,1,1,2-tetrafluoroethane (HFA 134a)**, 1,1,2-trifluoroethane (HFA 143), **1,1,1-trifluoroethane (HFA 143a)**, **difluoroethane (HFA 152a)**, **1,1,1,2,3,3,3-heptafluoropropane (HFA 227)** and the like. Preferred propellants are the hydrofluoroalkanes of the general formula: $C_xH_yF_z$ (I) in which x is the number 1, 2 or 3, y and z are each an integer $\geq 1$ and $y+z = 2x+2$. As a rule, those

hydrofluoroalkanes of the formula I in which x is the number 2 or 3 are particularly suitable (col. 7,m lines 8-10 and 25-40).

Keller discloses that the addition of a small amount of cosolvent can occasionally be advantageous. Suitable cosolvents include, for example, **water, alcohols having 1 to 3 carbon atoms**, with preferred examples including, **ethanol, propanol, isopropanol, ethylene glycol, propylene glycol, glycerol**, **glycerol**, or mixtures thereof. Ethanol is particularly preferred. In general, the proportion of cosolvents, if present, is **not over approximately 15% by weight**, **usually not over approximately 5% by weight**, based on the total formulation (col. 8, lines 64-67 and col. 9, lines 1-13).

Keller discloses that the aerosol formulations may also contain surface-active agents, including **polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, polyoxypropylene/polyoxyethylene block copolymers** in an amount from approximately 0.001 to 0.1% by weight, based on the total formulation (col. 9, lines 29-28). The compounds, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monostearate, and polyoxyethylene (20) sorbitan monooleate are polyoxyethylene fatty acid esters.

Keller discloses that the aerosol formulations may also contain buffer substances, including **citric acid and ascorbic acid** in amounts **ranging from 0.0001 to 1% by weight**, based on the total formulation (col. 9, lines 29-36). Citric acid and ascorbic acid are organic acids listed in the Markush group of claim 6. This disclosure meets the limitations of claim 6 and the limitation of claim 1, regarding an organic acid.

Keller discloses in Example 7 an aerosol suspension formulation that is transferred to an **aluminum container sealed with metered-dose valves** (i.e. a device for the administration of aerosol compositions), wherein the formulation comprises **tiotropium bromide (20g, ~0.03 wt.%)**, 10 g of nedocromil, 70 kg of a propellant mixture of **HFA 227 and HFA 134a**, which has been previously treated with 0.5 wt. % ethanol.

Although Keller's Example 7 does not include an inorganic or organic acid, Keller discloses that citric acid or ascorbic acid may be used as buffering compounds in the aerosol formulations. Therefore, the Examiner contends that all the limitations of claims 1, 6, and 15 are met, because Examples given in a disclosure are generally considered exemplary and not exclusive of other disclosures found within a prior art reference. Keller does not explicitly teach citric acid and ascorbic acid as organic acids, however, this would have been readily apparent to any person of ordinary skill in the art at the time of the instant invention.

**Claims 1-9, 11, 15, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Jager et al. (U.S. Patent No. 6,045,778).**

Jager discloses stabilized **medicinal aerosol solution formulations** comprising medicaments that degrade or decompose by interaction with solvents or water, an **HFC propellant**, a **cosolvent** and an **acid** (abstract).

Jager discloses that the HFC propellant must be toxicologically safe, have a vapor pressure suitable to enable the administration of the medicament from a pressurized metered dose inhaler (MDI), and be compatible with the components of the MDI device employed to administer the medicament. Preferred HFC propellants include **HFC-134a, HFC-227, HFC-**

**143a, HFC-134, HFC-152a, a mixture of two or more HFC propellants, or a mixture of at least one HFC propellant and one or more non-CFC propellant** (col. 2, lines 59-67 and col. 3, lines 1-4 and 11-16).

Jager discloses that small amounts of **water** may be added to the HFC propellant system in an amount **up to about 5 % by weight** (col. 3, lines 22-25).

Jager discloses that the medicament is present, in general, in an **amount from about 0.001 to 10% by weight** of the total weight of the formulation (col. 3, lines 63-65) and that preferred examples of medicaments for use in his aerosol solution formulations include **tiotropium bromide** (col. 4, lines 15-19). The medicaments in the formulation may be used in the form or either the free base or a pharmaceutically acceptable, non-toxic salt, thereof, including **bromide** (col. 4, line 45) and **iodide** (col. 4, line 48) (col. 4, lines 37-62).

Jager discloses examples of suitable cosolvents for use in his formulations include **alcohols** (e.g. ethanol, isopropanol), **glycols** (e.g. propylene glycol, polyethylene glycol, polypropylene glycol), **glycerol**, and **block copolymers of oxyethylene and oxypropylene**, and **polyoxyethylene fatty acid esters** (col. 5, lines 3-11).

Jager discloses that the acid for use in his formulations may be any **inorganic or mineral acid** (e.g. **hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid**) or an **organic acid** (e.g. **ascorbic acid and citric acid**) (col. 5, lines 30-37).

Jager discloses in Table 1 an aerosol formulation comprising ipratropium bromide **(0.001-2.5% w/w), ethanol (1.0-50.0% w/w), HFC-134a (50.0-99.0% w/w), an inorganic acid (0.01-0.00002 Normal), and water (0.0-5% w/w)**. This meets the limitations of claims 1,2, 7, 9, and 11, because the Jager's disclosures, cited above, state that tiotropium bromide may be

used as the medicament. The quantity of acid in Table 1 is given in units of Normality, which defines a **pH range equivalent to 2.0-4.7** in an aqueous system (col. 6, lines 17-19).

Jager discloses that a suitable device consists of an aerosol container and a 50-microliter aerosol-metering valve. The device is prepared by dispensing into an aerosol container, purging the headspace with nitrogen, sealing the container with valves, and pressure filling the sealed container with HFC-134a propellant (col. 9, lines 13-24).

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 13, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jager et al. (U.S. Patent No. 6,045,778).**

The teachings of Jager have been set forth above.

Jager does not explicitly teach an aerosol formulation comprising tiotropium bromide monohydrate, a device containing an aerosol formulation comprising tiotropium bromide monohydrate, nor a device in the form of a MDI comprising the composition of claim1.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention that one could use tiotropium bromide monohydrate in aerosol formulations, because Jager teaches the use of tiotropium bromide. The chemical compound name, tiotropium bromide, encompasses all tiotropium bromide salts, including tiotropium bromide monohydrate. Jager teaches devices containing ipratropium bromide (0.001-2.5% w/w), (ethanol (5-50% w/w), water (0-5% w/w), inorganic acid in an amount sufficient for a pH range of 2.0-4.7, and an HFC propellant. It would have been obvious to a skilled artisan that one could use tiotropium bromide monohydrate in lieu of ipratropium bromide, because Jager teaches tiotropium bromide as a suitable medicament for use in his invented aerosol formulations. Therefore, the formulation of Jager's table 1 renders claim 13 of the instant application obvious. Claims 17 and 19 are rendered obvious by Jager's teachings of a device comprising his invented formulations, an aerosol container, and aerosol metering valves. In addition, throughout Jager's disclosure, he repeatedly asserts that it is crucial that different formulation components are compatible with or

suitable for the administration from a MDI (col. 3, lines 28-30 and 41-43), the components of a MDI device (col. 2, lines 62-63 and col. 3, lines 28-30), and amenable for use with MDI solution formulations (col. 4, lines 63-66).

**Claims 10, 12, 14, 16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jager et al. (U.S. Patent No. 6,045,778) as applied to claims 13, 17, and 19 above, and further in view of Pairet et al. (US 2002/0122773).**

The teachings of Jager et al. have been set forth above.

Jager lacks the teaching of a composition comprising anhydrous crystalline tiotropium bromide, said composition free of water, and said composition contained in a device for administration of aerosol compositions.

Pairet teaches pharmaceutical compositions comprising anticholinergics (compound 1) and dopamine agonists (compound 2) (abstract). Anticholinergics (1) are preferably selected from **tiotropium salts**, oxitropium salts, and ipratropium salts [0010]. The salts of these (1) may have any of the following counter anions: **chloride, bromide, iodide, methane-sulphonate or para-toluenesulphonate** [0011]. Pharmaceutical compositions of 1 and 2 may be inhaled and includes inhalation aerosols and **inhalable solutions**, with a propellant, including **HFA-134a and HFA-227** [0026]. The proportion of the two active substances used relative to one another is variable [0033]. Pairet lists preferred dosage amounts in the instances when (1) is tiotropium bromide [0037] or tiotropium bromide monohydrate [0038]. The inhalation aerosol compositions may include additional excipients, including cosolvents and pH adjusters [0050], and may be administered using inhalers known in the art (e.g. MDIs) [0053]. Pairet teaches that crystalline tiotropium bromide monohydrate may be used [0101].

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Jager and Pairet, because both inventors teach pharmaceutical compositions for inhalation comprising tiotropium bromide, solvents, acids (i.e. pH adjusters), and HFC propellants. It would have been apparent to a skilled artisan from the teachings of Pairet that one could use the anhydrous crystalline form of tiotropium bromide, because it differs from crystalline tiotropium bromide monohydrate by one water molecule of hydration. Jager teaches formulations than may comprise 0% water, thus obviating compositions comprising tiotropium bromide or its monohydrate that are free of water. A skilled artisan would have had a reasonable expectation of successfully combining the teachings of Jager and Pairet, due to the similarities of the compositions taught by both inventors (i.e. common components) and the same intended route of administration of said compositions using inhalers, such as MDIs.

**Claims 1-5, 7-9, 15, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hassan et al. (WO 00/47200) in view of Lewis et al. (US 2002/0183293).**

Hassan teaches a medicament containing (A) formoterol or a pharmaceutically acceptable salt or solvate thereof and (B) a **tiotropium salt of a pharmaceutically acceptable acid** for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease (abstract).

Hassan teaches that the tiotropium salt is preferably tiotropium methane sulphonate or tiotropium bromide (page 3, lines 1-3). Administration is preferably by inhalation of (A) and (B) in admixture or separately in a nebulizable **aqueous**, **organic**, **aqueous/organic solution** medium or by inhalation of an **aerosol** comprising (A) and (B) in **solution or dispersion in a propellant** (page 3, 2nd paragraph). Acceptable propellants include **HFA-134a, HFA-227**, or

mixtures of two or more halogen substituted hydrocarbons. The aerosol may contain **up to 5% by weight** of the composition of the **active ingredient**, for example, **0.002 to 5% by weight** (page 3, third paragraph). The aerosol composition may also contain a **cosolvent**, such as **ethanol** in an amount **up to 30% by weight** of the composition, particularly for administration from a pressurized **metered dose inhalation device** (page 4, lines 1-3).

Hassan teaches a kit comprising one or more **inhalation devices** for administration of (A) and (B), including a metered dose inhaler containing an aerosol comprising (A) in a propellant and another **metered dose inhaler containing (B) in a propellant** (page 7, second paragraph).

Hassan lacks the teaching of compositions comprising an inorganic acid.

Lewis teaches an **aerosol solution** composition for use in an aerosol inhaler comprises an active material, a propellant containing a **hydrofluoroalkane**, a **cosolvent** and optionally a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. The composition is stabilized by using mineral acid (abstract).

Lewis teaches an embodiment of the invention, regarding a pressurized MDI for administering pharmaceutical doses filled with a pharmaceutical composition consisting of a solution of formoterol fumarate in **HFA 134a**, **12% w/w ethanol**, and optionally isopropyl myristate in an amount less/equal than 1.0% w/w. The apparent **solution pH** was adjusted **to between 3.0 and 3.5** by addition of small amounts of **hydrochloric acid**. The expression "% w/w" means the weight percentage of the component in respect to the total weight of the composition [0021].

Lewis teaches that the active ingredients may include long-acting beta2-adrenergic agonists, including formoterol, **combinations with** steroids (e.g. fluticasone propionate) or with anticholinergic atropine like derivatives (e.g. **tiotropium bromide**) [0040].

Lewis teaches that the hydrocarbon propellant may be **HFA-134a, HFA-227, or mixtures thereof** [0048]. The cosolvent used in the compositions is preferably an alcohol, especially **ethanol** [0049]. The compositions may also contain a low volatility component, including **propylene glycol, polyethylene glycol, glycerol**, residual **water (less than 0.1% w/w)**, and esters of long-chain fatty acids, wherein the low volatility component is present in amounts from 0.1 to 10% w/w [0051] to [0052]. The apparent pH of the compositions is **between 2.5 and 5.0** and strong mineral acids, including **hydrochloric, nitric, and phosphoric acid** are used to adjust the pH [0054]. Lewis teaches in claims 3, 4, and 12 of his application that the compositions are filled into a container/device and closed via crimping with valves.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Hassan and Lewis, because both inventors teach pharmaceutical compositions comprising formoterol and tiotropium bromide, HFA propellants, and solvent for use in inhaler devices (e.g. metered dose inhalers). A skilled artisan would have been further motivated to combine the teachings of Hassan and Lewis, because Lewis teaches that mineral acids are added to stabilize the compositions. Regarding the amounts of compounds, the combined teachings of Hassan and Lewis teach amounts of solvent and tiotropium bromide that encompasses or is obvious over the stated ranges cited in the claims of the instant application. Furthermore, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely

optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 1-6 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/392,559 (copending '559).** Although the conflicting claims are not identical, they are not patentably distinct from each other because the recited compositions of claims 1-6 of copending '559 have substantially the same components as the compositions of

claims 1-6, 8, 9, and 10 of the instant application, such as tiotropium bromide or one of its derivatives (e.g. anhydrous crystalline tiotropium bromide monohydrate), alcohols (i.e. solvents), inorganic acids, and organic acids. In addition, it is noted that copending '559 has different inventors than the instant application, but the **same assignee**.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Claims 1-6, 8, 9, and 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/400,127 (copending '127).** Although the conflicting claims are not identical, they are not patentably distinct from each other because the recited compositions of claims 1-6 of copending '127 have substantially the same components as the compositions of claims 1-6, 8, 9, and 10 of the instant application, such as anhydrous crystalline tiotropium bromide, alcohols (i.e. solvents), inorganic acids, and organic acids.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Claims 1 and 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 8 of copending Application No. 10/976,624 (copending '624) in view of Lewis et al. (US 2002/0183293).** The cited claims of the instant application and claims 1, 2, and 8 of copending '624 are both drawn to compositions comprising tiotropium bromide or a derivative thereof (e.g.

anhydrous crystalline tiotropium bromide) and a pharmaceutically acceptable carrier, including propellants. Copending '624 does not recite specific propellants, however it is understood that the term propellant encompasses HFC propellants. Another difference between the applications is that copending '624 does not recite the inclusion of inorganic or organic acids in the formulation. Lewis teaches that mineral acids (i.e. inorganic acids, such as hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid) may be added to pharmaceutical aerosol compositions comprising formoterol and tiotropium bromide, as well as HFC propellants. Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that mineral acids could be added to similar compositions with a reasonable expectation of obtaining a viable pharmaceutical formulation.

This is a provisional obviousness-type double patenting rejection.

**Claims 1-3, 15, and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9, 22-24, 27, and 29 of copending Application No. 10/976,688 (copending '688) in view of Lewis et al. (US 2002/0183293).** The cited claims of the instant application and claims 9, 22-24, 27, and 29 of copending '688 are both drawn to pharmaceutical compositions comprising tiotropium salts (e.g. tiotropium bromide) and solvates thereof and a pharmaceutically acceptable carrier, including propellants. Copending '688 does not recite specific propellants, however it is understood that the term propellant encompasses HFC propellants. Another difference between the applications is that copending '688 does not recite the inclusion of inorganic or organic acids in the formulation. Lewis teaches that mineral acids (i.e. inorganic acids, such as hydrochloric acid,

sulfuric acid, nitric acid, and phosphoric acid) may be added to pharmaceutical aerosol compositions comprising formoterol and tiotropium bromide, as well as HFC propellants. Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that mineral acids could be added to similar compositions with a reasonable expectation of obtaining a viable pharmaceutical formulation.

This is a provisional obviousness-type double patenting rejection.

**Claims 1-3, 15, and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 21-23, 26, and 28 of copending Application No. 10/977,753 (copending '753) in view of Lewis et al. (US 2002/0183293).** The cited claims of the instant application and claims 12, 21-23, 26, and 28 of copending '753 are both drawn to pharmaceutical compositions comprising tiotropium salts (e.g. tiotropium bromide) and solvates thereof and a pharmaceutically acceptable carrier, including propellants. Copending '753 does not recite specific propellants, however it is understood that the term propellant encompasses HFC propellants. Another difference between the applications is that copending '753 does not recite the inclusion of inorganic or organic acids in the formulation. Lewis teaches that mineral acids (i.e. inorganic acids, such as hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid) may be added to pharmaceutical aerosol compositions comprising formoterol and tiotropium bromide, as well as HFC propellants. Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that mineral acids could be added to similar compositions with a reasonable expectation of obtaining a viable pharmaceutical formulation.

This is a provisional obviousness-type double patenting rejection.

**Claims 1-8, and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 and 24 of copending Application No. 11/169,876 (copending '876).** Although the conflicting claims are not identical, they are not patentably distinct from each other because the recited compositions of claims 1-19 and 24 of copending '876 have substantially the same components as the compositions of claims 1-6, 8, 9, and 10 of the instant application, such as anhydrous crystalline tiotropium bromide, alcohols (i.e. solvents), inorganic acids, and organic acids. The variation of the amount of water in the compositions at concentrations of parts per million is obvious, because the optimization of the amounts of components in a formulation is routinely practiced in the art. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Other Matter***

The Examiner notes that Applicant used the abbreviation for hydrofluorocarbon, HFC, in claim 1. The Examiner suggests writing out the word hydrofluorocarbon followed by its abbreviation in parentheses.

*Conclusion*

**The specification and claim 8 are objected. All claims are rejected. No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Examiner

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER